Para-Selective C–H Amidation of Simple Arenes with Nitriles

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A *para*-selective C–H amidation of simple arenes with nitriles has been developed. By increasing the amount of arenes, a further *meta*-selective C–H arylation of the produced amides occurred. Both steric and electronic effects are utilized to control the selectivity, resulting in only *para*-selective amidation products. The readily available nitriles as amidation reagents instead of amides make the synthesis of *N*-arylamides more accessible.

Keywords: amidation; nitriles; arenes; copper

The ubiquitous presence of *N*-arylamides in natural products, biologically active molecules and organic functional materials makes them valuable synthetic targets.[1,2] The Goldberg reaction[2] is one of the most common methods for the synthesis of *N*-arylamides, but it requires prefunctionalization of arenes to aryl halides. Therefore, extensive efforts have been devoted to the synthesis of *N*-arylamides via C–H amidation of arenes. Over the last few years, there have been tremendous advances in the field of C-H amination and amidation of arenes.[3-10] Highlights include the amidation of arenes bearing directing groups which has been achieved by Li,[5a] Shen,[5b] Yu and Che,[5c,7a,7b] Ribas and Stahl,[5d,e] Chen,[6a,b] Daugulis,[6c] Buchwald,[6d] Chang,[7c] Glorius,[7d] and Zhu[7e] et al. (Scheme 1a), and the amidation of activated arenes such as heterocycles and polyfluoroarenes as developed by Schreiber and co-workers (Scheme 1b).[8] In contrast, the C–H amidation of simple arenes remains a challenge because of poor reactivity and selectivity. In 2011, the metal-free oxidative amidation of simple arenes using solely PhI(OAc)₂ as oxidant was reported independently by the Cho and Chang,[9a] DeBoef,[9b] and Antonchick[9c] groups [Scheme 1c, (1)]. However, most of the reactions were resulted in a mixture of several isomers. Recently, Hartwig[10a] and DeBoef[10b] groups achieved regioselective amidation of simple arenas using respectively Pd(OAc)₂ and Au(I) as a catalyst [Scheme 1c, (2)].

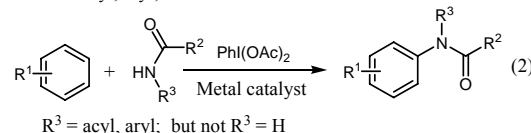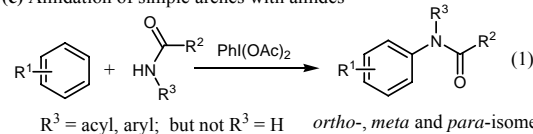(a) Amidation of arenes bearing directing groups with amides
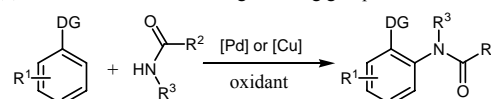
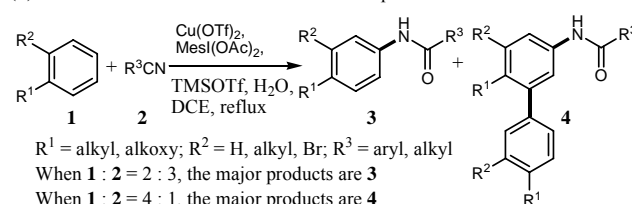(b) Amidation of activated arenes with amides
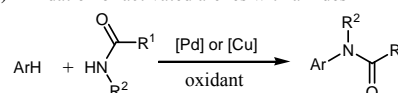
ArH = heterocyctes, polyfluoroarenes *et al.*

(c) Amidation of simple arenes with amides

R³ = acyl, aryl; but not R³ = H   *ortho-*, *meta* and *para*-isomers (1)

R³ = acyl, aryl; but not R³ = H (2)

Hartwig' work: Pd catalyst, *meta* and *para*-isomers
DeBoef' work: Au catalyst, *para*-selective products

(d) *This work*: *Para*-selective amidation of simple arenes with nitriles

R¹ = alkyl, alkoxy; R² = H, alkyl, Br; R³ = aryl, alkyl
When **1** : **2** = 2 : 3, the major products are **3**
When **1** : **2** = 4 : 1, the major products are **4**
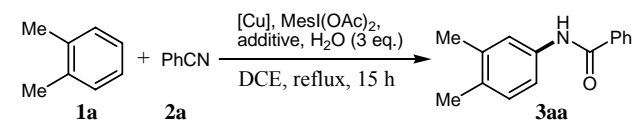
Scheme 1. C–H amidation of arenes.

However, in all of the above mentioned amidation reactions of simple arenes, only substrates with strong-acidic N-H bond have been employed as amidation reagents, such as *N*-arylamides and imides. The weak nucleophilicity of *N*-unsubstituted amides under acidic or neutral conditions leads to their poor reactivity in the amidation reactions.[5e] Therefore, it is very difficult to synthesize *N*-monosubstituted

amides by C-H amidation of simple arenes using amides as the amidation reagents.

Nitriles are employed widely as nitrogen nucleophilic reagents under acidic conditions in Ritter reactions,[11] which means nitriles may have a better reactivity than *N*-unsubstituted amides in amidation reactions of simple arenes under acid conditions. Furthermore, our and others' recent work[12] also indicated that use of nitriles as nitrogen nucleophiles instead of amides can make the synthesis of *N*-arylamides more accessible, because many amides are readily prepared from nitriles by hydrolysis. Such results stimulated us to explore the feasibility of C-H amidation of simple arenes with nitriles. Herein, we report a *para*-selective C–H amidation of simple arenes using nitriles as the amidation reagents.[10c] When the amount of arene was increased to four equivalents, a further *meta*-selective C–H arylation of the produced amides occurred, resulting in tandem C−N and C−C bond formation (Scheme 1d).

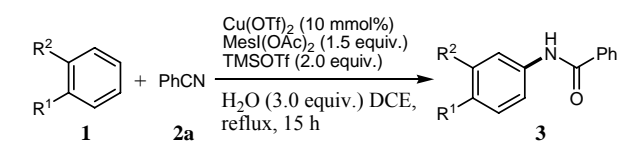**Table 1.** Optimization of reaction conditions.[a]

entry	[Cu] (mmol%)	MesI(OAc)$_2$ (equiv.)	additive (equiv.)	yield (%)
1	Cu(OTf)$_2$ (10)	1.5	BF$_3$•Et$_2$O (2.0)	0
2	Cu(OTf)$_2$ (10)	1.5	HOTf (2.0)	64
3	Cu(OTf)$_2$ (10)	1.5	TsOH (2.0)	0
4	Cu(OTf)$_2$ (10)	1.5	TMSOTf (2.0)	74
5	CuOTf (10)	1.5	TMSOTf (2.0)	72
6	Cu(OAc)$_2$ (10)	1.5	TMSOTf (2.0)	60
7	CuBr (10)	1.5	TMSOTf (2.0)	68
8	CuI (10)	1.5	TMSOTf (2.0)	72
9	none	1.5	TMSOTf (2.0)	0
10[b]	**Cu(OTf)$_2$ (10)**	**1.5**	**TMSOTf (2.0)**	**83**
11[b]	Cu(OTf)$_2$ (10)	1.5	TMSOTf (2.5)	64
12[b]	Cu(OTf)$_2$ (10)	1.5	TMSOTf (1.5)	64
13[b]	Cu(OTf)$_2$ (10)	2.0	TMSOTf (2.0)	74
14[b]	Cu(OTf)$_2$ (10)	1.3	TMSOTf (2.0)	75
15[b]	Cu(OTf)$_2$ (5)	1.5	TMSOTf (2.0)	69
16[b,c]	Cu(OTf)$_2$ (10)	1.5	TMSOTf (2.0)	71
17[b,d]	Cu(OTf)$_2$ (10)	1.5	TMSOTf (2.0)	44

[a] Reaction Conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), catalyst, MesI(OAc)$_2$ (0.45 mmol), additive, H$_2$O (0.9 mmol), DCE (2.0 mL, contains 0.1% v/v H$_2$O), reflux, 15 h, under Ar. The yields were isolated yields. [b] H$_2$O was added after 2 h. [c] 0.36 mmol of **2a** was used. [c] The reaction was carried out at 70 ˚C.

We began to investigate the C-H amidation of *o*-xylene **1a** with benzonitrile **2a** using Cu(OTf)$_2$ as a catalyst, MesI(OAc)$_2$ as an oxidant and DCE as the solvent under reflux conditions. The variation of the acids indicated TfOH could effectively promote the reaction to give the product **3aa** in a yield of 64%

(entries 1-3, Table 1). Use of TMSOTf as an additive instead of TfOH could increase the yield to 74% (entry 4, Table 1). The screening of copper salts revealed that Cu(OTf)$_2$ was superior to all others tested (entries 4-8, Table 1). No desired product was observed in the absence of a copper catalyst (entry 9, Table 1). In consideration of the decomposition of some of TMSOTf into HOTf in the presence of H$_2$O, we decided to add H$_2$O to the reaction after two hours, because at that time TMSOTf had been consumed to generate the diaryliodonium salts **5** instead of being decomposed into HOTf based on the reaction mechanism in Scheme 3. As expected, the best yield of 83% was obtained if H$_2$O was added after two hours (entry 10, Table 1). Adjustment of the amount of MesI(OAc)$_2$ and TMSOTf did not improve the yield of **3aa** (entries 11-14, Table 1). A lower loading of catalyst or benzonitrile **2a** led to a lower yield of **3aa** (entries 15-16, Table 1). An attempt to reduce the temperature to 70 ˚C resulted in a significantly decreased yield of **3aa** (entry 17, Table 1). It is notable that only the *para*-selective isomer was observed by ^{1}H NMR on the crude reaction mixture.
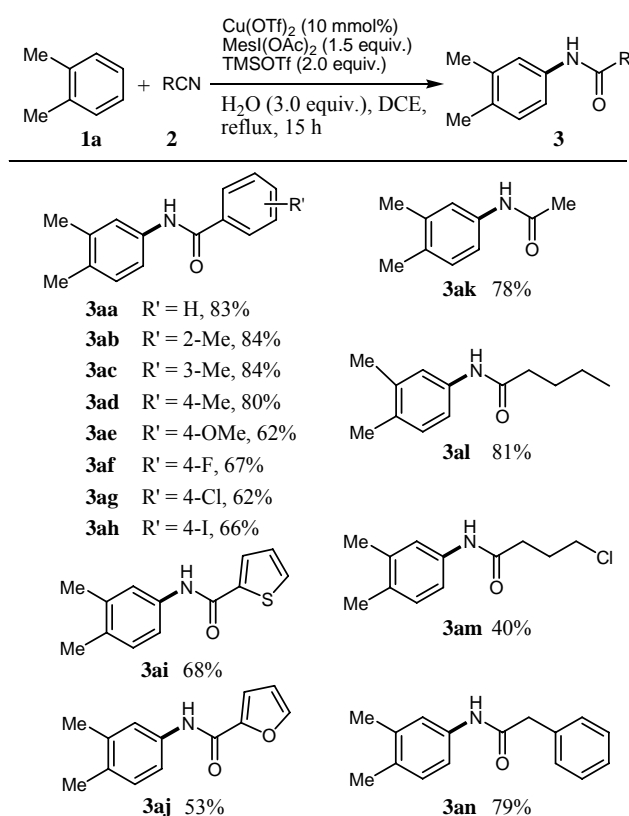
Table 2. Substrate scope of simple arenes.[a]

[a] Reaction Conditions: **1** (0.3 mmol), **2a** (0.45 mmol), Cu(OTf)$_2$ (0.03 mmol), MesI(OAc)$_2$ (0.45 mmol), TMSOTf (0.6 mmol), H$_2$O (0.9 mmol), DCE (2.0 mL, contains 0.1% v/v H$_2$O), reflux, 15 h, under Ar. H$_2$O was added after 2 h. The yields were isolated yields. [b] The reaction was carried out for 24 h.

To explore the substrate scope of simple arenes, benzonitrile **2a** was selected to react with a range of substituted arenes **1** under standard conditions. Both mono- and disubstituted simple arenes could undergo the amidation reaction to generate the corresponding *N*-arylamides in moderate to high yields with high regioselectivities (35-93%, Table 2). The amidation reactions occurred *para* to the activating *ortho*-/*para*-directing substituents, when monosubstituted benzenes were deployed in this reaction (**3da**, **3ea**,

3fa and **3ga**, Table 2). Stronger *ortho-*/*para*-directors dominated and directed the regioselectivities when disubstituted benzenes were employed as the substrates. The amidation reactions occurred *para* to the stronger *ortho-*/*para*-directing substituents (**3ba** and **3ca**, Table 2). Cumene **1f** and *tert*-butylbenzene **1g** gave low yields, maybe because of Friedel-Crafts dealkylation of the substrates (**3fa** and **3ga**, Table 2). Use of *m*-xylene **1h** as a substrate afforded a low yield, indicating that the reaction is sensitive to steric effects (**3ha**, Table 2). 1, 2, 3, 4-Tetrahydronaphthalene **1i** underwent this transformation to generate the *para*-selective amidation product **3ia** in a yield of 66% (**3ia**, Table 2). All of the above demonstrate that the regioselectivities of such amidation reactions are clearly controlled by both steric and electronic effects, resulting in the isolation of only *para*-selective amidation products. Other isomers were not observed in each case by ^{1}H NMR on the crude reaction mixture. It is regretful that electron-deficient arenes could not undergo this reaction to get the desired products, such as chlorobenzene and nitrobenzene.

Table 3. Substrate scope of nitriles.[a]

3aa	R' = H, 83%	
3ab	R' = 2-Me, 84%	
3ac	R' = 3-Me, 84%	
3ad	R' = 4-Me, 80%	
3ae	R' = 4-OMe, 62%	
3af	R' = 4-F, 67%	
3ag	R' = 4-Cl, 62%	
3ah	R' = 4-I, 66%	

3ak 78%

3al 81%

3ai 68%

3am 40%

3aj 53%

3an 79%

[a] Reaction Conditions: **1a** (0.3 mmol), **2** (0.45 mmol), Cu(OTf)$_2$ (0.03 mmol), MesI(OAc)$_2$ (0.45 mmol), TMSOTf (0.6 mmol), H$_2$O (0.9 mmol), DCE (2.0 mL, contains 0.1% v/v H$_2$O), reflux, 15 h, under Ar. H$_2$O was added after 2 h. The yields were isolated yields.

To investigate the substrate scope of the nitriles, *o*-xylene **1a** was selected as the partner to react with different nitriles. The results in Table 3 show that both aryl nitriles and aliphatic nitriles could undergo this transformation to generate the desired products in moderate to excellent yields (40-84%). Substituted benzonitriles bearing both electron-donating and electron-withdrawing groups smoothly underwent this reaction generating the desired products **3** in good yield (**3aa-3ah**, Table 3). It is notable that the reaction was not affected by steric effects of the nitriles (**3ab**, **3ac** and **3ad**, Table 3). Substituted benzonitriles with F, Cl or I smoothly led to corresponding amides with the halogen substituents intact (**3af**, **3ag** and **3ah**, Table 3). The heterocyclic aromatic nitriles **2i**, **2j** also sucessfully underwent the reaction to afford the desired products **3ai**, **3aj** in yields of 68%, 53%, respectively (**3ai** and **3aj**, Table 3). High yields were obtained when aliphatic nitriles **2k**, **2l** and **2n** were selected as the substrates (**3ak**, **3al** and **3an**, Table 3). Pleasingly, the aliphatic nitrile **2m** smoothly underwent this transformation, revealing that the halogen substitutes were compatible under such reaction conditions (**3am**, Table 3). In addition, other isomers were not observed except the *para*-selective product in each case by ^{1}H NMR on the crude reaction mixture.

Table 4. *Para*-selective amidation of *o*-xylene **1a** with nitriles **2**, followed by *meta*-selective arylation of produced *N*-arylamides with another *o*-xylene **1a**.[a]


4a R = H, 50 %	**4b** R = 4-Me, 40 %	**4c** R = 3-Me, 46 %
4d R = 4-Cl, 51 %	**4e** R = 4-F, 50 %	**4f** R = 4-I, 36 %
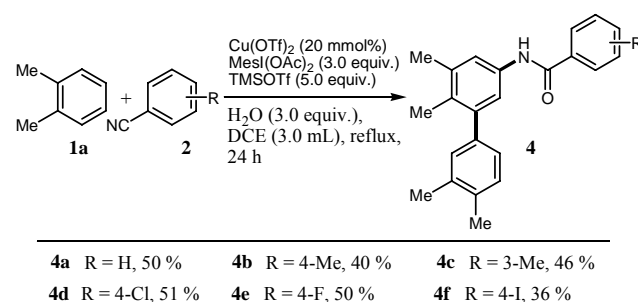
[a] Reaction Conditions: **1a** (1.2 mmol), **2** (0.3 mmol), Cu(OTf)$_2$ (0.06 mmol), MesI(OAc)$_2$ (0.9 mmol), TMSOTf (1.5 mmol), H$_2$O (0.9 mmol), DCE (3.0 mL, contains 0.1% v/v H$_2$O), reflux, 24 h, under Ar. H$_2$O was added after 3 h. The yields were isolated yields.

By increasing the amount of arene to four equivalents, we were surprised to find that further arylation of the produced *N*-arylamides occurred selectively at the *meta*-position of the aromatic ring (Table 4).[13] A variety of aryl nitriles were selected to react with *o*-xylene **1a**. The results revealed that benzonitriles bearing both electron-donating and electron-withdrawing groups smoothly underwent the multi-step transformation to generate the corresponding products **4** in moderate yields (**4a-4f**, Table 4).

Some control experiments were carried out to understand the mechanism of the amidation reaction (Scheme 2 and Figure 1). It was found that no product was detected when using benzamide to react with *o*-xylene **1a** instead of benzonitrile according to our standard condition (eqn. 1, Scheme 2). It

excluded the possibility of amide involved in the reaction through hydrolysis from nitriles according to the similar mechanism reported recently by us.[12a,b] The diaryliodonium salt **5a** was employed to react with benzonitrile **2a** to get the corresponding product **3aa** in a yield of 81% (eqn. 2, Scheme 2). It meant the diaryliodonium salt **5a** may be an intermediate of this transformation.[14] In addition, the isotopic labelling experiment of use of $H_2^{18}O$ revealed that the water was indeed involved in this reaction (eqn. 3, Scheme 2).
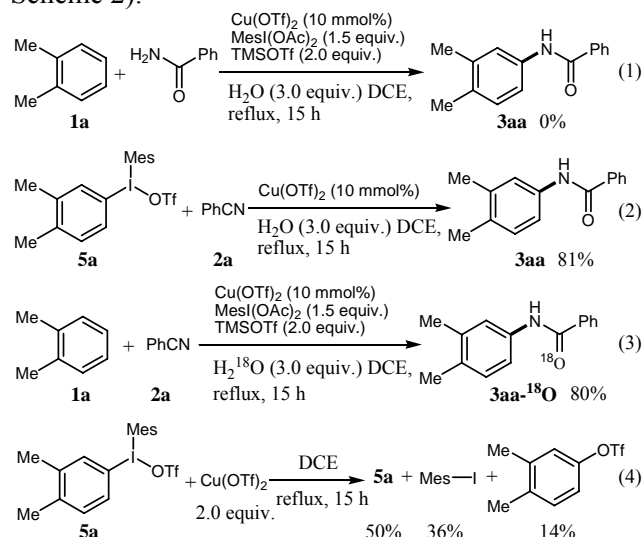
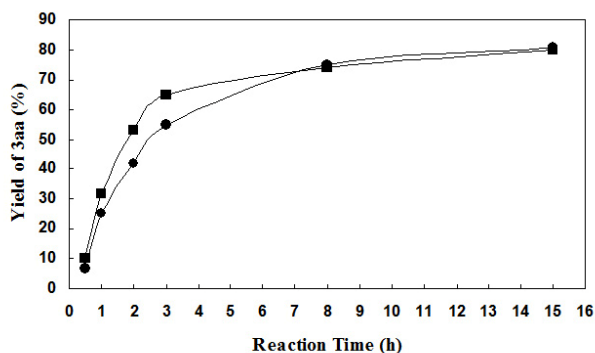**Scheme 2.** Mechanistic experiments.

Figure 1. Yield of **3aa** as a function of time in the reaction of diaryliodonium salt **5a** with benzonitrile **2a** catalyzed by CuOTf and Cu(OTf)$_2$. ■ = CuOTf, ● = Cu(OTf)$_2$. Reaction Conditions: diaryliodonium salt **5a** (0.3 mmol), benzonitrile **2a** (0.45 mmol), [Cu] (0.03 mmol), H$_2$O (0.9 mmol), DCE (2.0 mL, contains 0.1% v/v H$_2$O), reflux, under Ar. The yields were isolated yields.

However, an attempt to prepare the Cu(III) intermediates **B** in scheme 3 to evaluate the following transformations failed maybe because of the instability of it (eqn. 4, Scheme 2). The literature indicated only a few stable organocopper(III) complexes have been obtained.[15] Instead, diaryliodonium salt **5a** (recovery rate of 50%), 2-

iodomesitylene (yield of 36%) and 3, 4-dimethylphenyl trifluoromethanesulfonate (yield of 14%) were acquired. In order to prove the possible active copper catalyst, we monitored the kinetics of the reaction (Figure 1). The result indicated CuOTf was more active than Cu(OTf)$_2$, which implied that CuOTf may be active catalyst.

On the basis of the experimental results, a possible catalytic mechanism for this transformation is illustrated in Scheme 3.[13b,16] Initially, the TMSOTf-promoted electrophilic aromatic substitution of arenes with MesI(OAc)$_2$ generates the diaryliodonium salts **5**. The active catalyst CuOTf, formed from Cu(OTf)$_2$ through the disproportionation or reduction, is oxidized to the intermediates **B** by the diaryliodonium salts **5**. The intermediates **B** undergo a ligand exchange with nitriles **2** to afford the intermediates **C**. Proposed Cu(III) species promote the hydrolysis of coordinated nitriles into intermediates **D**, which then undergo a reductive elimination to yield the final products **3** and release the catalyst CuOTf to complete the catalytic cycle.
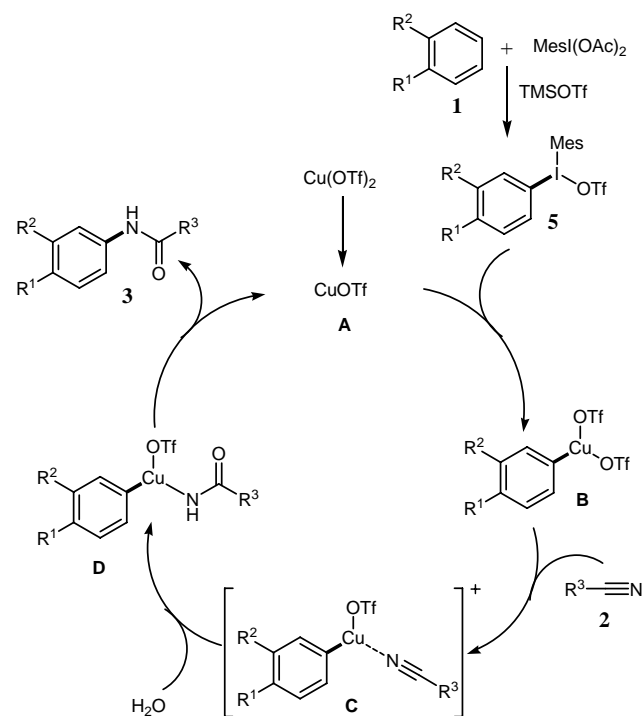
Scheme 3. Proposed catalytic mechanism.

In summary, we have developed a copper-catalyzed highly *para*-selective C–H amidation of simple arenes using nitriles as the amidation reagents. When the amount of arenes was increased to four equivalents, a further *meta*-selective C–H arylation of the produced amides occurred, resulting in tandem C−N and C−C bonds formation. Both steric and electronic effects were utilized to control the selectivity, resulting in only *para*-selective amidation products. *N*-Monosubstituted amides can be synthesized with this approach, which both complements and extends the previous scope of

applicable substrates. Given the use of readily available nitriles as amidation reagents (instead of amides), this route allows for the facile synthesis of *N*-arylamides. Further studies on other reactions of nitriles and the applications are now ongoing in our laboratory.

Experimental Section

General procedure for the synthesis of *N*-(3, 4-Dimethylphenyl)benzamide **3aa**: $Cu(OTf)_2$ (10.8 mg, 0.03 mmol), $MesI(OAc)_2$ (163.8 mg, 0.45 mmol) were placed into a 25 mL Schlenk tube equipped with a magnetic stir bar. To this mixture was added in sequence DCE (2.0 mL, contains 0.1% v/v H_2O), *o*-xylene **1a** (36 uL, 0.3 mmol), benzonitrile **2a** (46 uL, 0.45 mmol), TMSOTf (108 uL, 0.6 mmol) with an injection syringe under stirring and an argon atmosphere. After the reaction mixture was stirred for 2 h at reflux, water (16 uL, 0.9 mmol) was added with an injection syringe and the mixture was stirred for additional 13 h at reflux under an argon atmosphere. The solution was cooled to room temperature and was quenched by the addition of 20 mL water and extracted with dichloromethane (3×10 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluent: petroleum ether / ethyl acetate / dichloromethane = 10 : 1 : 1) to afford 56.0 mg (83%) of **3aa**; IR:(KBr) ν_{max} 3304, 1649, 1591, 1528, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.87-7.84 (m, 2H), 7.76 (s, 1H), 7.57-7.44 (m, 4H), 7.35 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz 1H), 7.12 (d, J = 8.4 Hz, 1H), 2.27 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.6, 137.3, 135.5, 135.1, 133.0, 131.7, 130.0, 128.7, 126.9, 121.5, 117.7, 19.9, 19.2; HRMS m/z (ESI): Calcd. for $C_{15}H_{16}NO$ [M+H]$^+$ 226.1226, Found: 226.1226.

Acknowledgements

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R^1 = alkyl, alkoxy; R^2 = H, alkyl, Br; R^3 = aryl, alkyl
When **1** : **2** = 2 : 3, the major products are **3**
When **1** : **2** = 4 : 1, the major products are **4**